

Table S1. Gut hormones, glucose and insulin responses during the mixed meal tolerance test

Gut hormone	Group	Pre-op visit n=24	2 weeks post-op n=24	p ^a	20% weight loss time point (n=24)	p ^b
Peak active GLP-1 (pmol/L)	Standard Limb	24 ± 33	78 ± 41	0.34	70 ± 32	0.43
	Long Limb	16 ± 13	62 ± 30		70 ± 19	
Active GLP-1 AUC (pmol·min/L)	Standard Limb	2574 ± 4082	5338 ± 3968	0.68	5312 ± 3711	0.18
	Long Limb	1384 ± 1404	4528 ± 1764		3812 ± 1327	
Peak total GLP-1 (pmol/L)	Standard Limb	13 ± 6	105 ± 49	0.48	117 ± 57	0.68
	Long Limb	14 ± 10	96 ± 33		112 ± 38	
Total GLP-1 AUC (pmol·min/L)	Standard Limb	1017 ± 394	6190 ± 2566	0.68	6281 ± 2586	0.71
	Long Limb	1044 ± 543	6487 ± 1987		6039 ± 2555	
Peak concentration of PYY (pmol/L)	Standard Limb	56 [31, 75]	125 [106, 151]	0.26	104 [85, 158]	0.29
	Long Limb	33 [27, 69]	115 [90, 154]		101 [74, 120]	
PYY concentrationAUC (pmol·min/L)	Standard Limb	6012 [5310, 10072]	12583 [11336, 14536]	0.55	14472 [10444, 16385]	0.78
	Long Limb	7348 [6563, 9986]	13054 [11073, 15911]		11189 [5514, 12851]	
Peak concentration of total GIP (pmol/L)	Standard Limb	75 [39, 110]	120 [40, 205]	0.69	129 [61, 259]	0.20
	Long Limb	101 [31, 171]	110 [76, 160]		88 [38, 181]	
GIP concentration AUC (pmol·min/L)	Standard Limb	5276 [1219, 9671]	4329 [1537, 11941]	0.22	9185 [4006, 15486]	0.69
	Long Limb	11641 [1965, 14666]	9184 [4782, 9829]		6041 [4174, 11893]	
Peak plasma glucose (mmol/L)	Standard Limb	15.3 [13.2, 17.2]	10.3 [8.7, 12.6]	0.76	9.3 [7.7, 11.0]	0.32
	Long Limb	14.4 [11.4, 17.5]	10.5 [8.9, 11.1]		8.0 [6.9, 9.3]	
Plasma glucose AUC (mmol·min/L)	Standard Limb	2828 [2450, 3172]	1828 [1553, 2189]	0.66	1564 [1276, 1896]	0.38
	Long Limb	2647 [2103, 3221]	1862 [1632, 2006]		1301 [1170, 1580]	
Incremental plasma glucose AUC (mmol·min/L)	Standard Limb	509 ± 250	517 ± 180	0.02	491 ± 212	0.01
	Long Limb	470 ± 197	394 ± 131		335 ± 140	
Peak serum insulin (mU/L)	Standard Limb	29 ± 14	37 ± 16	0.93	42 ± 20	0.37
	Long Limb	28 ± 16	36 ± 21		38 ± 18	
Serum insulin AUC (mU·min/L)	Standard Limb	5281 ± 2464	6259 ± 3088	0.89	6433 ± 3058	0.34
	Long Limb	5128 ± 2833	6037 ± 3481		5716 ± 2879	

Continuous data presented as mean ± SD when normally distributed or median [interquartile range] when non-normally distributed. Statistical test used: ANCOVA. p-values refer to comparing Long Limb versus Standard Limb outcomes at 2 weeks post-op visit (p^a) and 20% weight loss visit (p^b). Differences adjusted for outcome at baseline. GLP-1 – glucagon-like peptide-1, PYY – peptide YY. GIP – gastric inhibitory polypeptide. AUC – area under the curve, calculated from time point 0 to 120 mins for all values but glucose where AUC was calculated from time point 0 to 180 mins.

Table S2. Rate of glucose appearance and disappearance in the hyperinsulinaemic-euglycaemic clamps

Variable	Group	Pre-op visit (n=23)	2 weeks post-op (n=23)	p^a	20% weight loss time point (n=23)	p^b
Ra low (umol/min/kg)	Standard Limb	5.1 ± 1.7	3.4 ± 0.9	0.94	2.8 ± 1.3	0.62
	Long Limb	5.0 ± 2.4	3.4 ± 1.4		2.6 ± 1.7	
Ra high (umol/min/kg)	Standard Limb	1.9 ± 2.4	0.6 ± 1.7	0.86	0.0 ± 1.8	0.09
	Long Limb	1.1 ± 2.0	0.7 ± 1.7		-1.0 ± 1.3	
Rd low (umol/min/kg)	Standard Limb	9.8 ± 1.6	11.8 ± 2.9	0.18	15.2 ± 2.9	0.36
	Long Limb	10.6 ± 3.6	13.6 ± 4.2		16.5 ± 4.1	
Rd high (umol/min/kg)	Standard Limb	18.7 ± 7.6	29.0 ± 9.1	0.98	36.1 ± 8.5	0.47
	Long Limb	19.1 ± 9.4	29.8 ± 9.8		38.1 ± 9.2	

Continuous data presented as mean ± SD when normally distributed. Statistical test used: ANCOVA. p-values refer to comparing Long Limb versus Standard Limb outcomes at 2 weeks post-op visit (p^a) and 20% weight loss visit (p^b). Differences adjusted for outcome at baseline. Ra: rate of glucose appearance. Rd: rate of glucose disappearance. Low: measured in the phase of low-dose insulin infusion. High: measured in the phase of high-dose insulin infusion.

Table S3. Glucose-lowering medications

Characteristic	Long Limb RYGB Baseline n=26	Standard Limb RYGB Baseline n=27	Long Limb RYGB 1-year post-operatively n=26	Standard Limb RYGB 1-year post-operatively n=26
Number of glucose-lowering medications at baseline (classes)				
1	11% (3)	4% (1)	0	0
2	27% (7)	44% (12)	0	0
3	35% (9)	26% (7)	1	0
4	27% (7)	19% (5)	0	0
5	0% (0)	7% (2)	0	0
Classes of medications				
Biguanides	92% (24)	93% (25)	1	0
SGLT-2 inhibitors	54% (14)	56% (15)	1	0
Sulfonylurea	50% (13)	48% (13)	0	0
GLP-1 agonists	35% (9)	15% (4)	1	0
DPP-4 inhibitors	31% (8)	52% (14)	0	0
Insulin	15% (4)	15% (4)	0	0
Total	72	75		

Categorical data presented as percentage (n). RYGB – Roux-en-Y gastric bypass. SGLT-2 – sodium-glucose transport protein-2. GLP-1 – glucagon-like peptide-1. DPP-4 – dipeptidyl peptidase-4 inhibitor.

Figure S1. A: Glycated haemoglobin; B: total body weight loss; C: T2D remission in the first post-operative year. Data expressed as means \pm SD. N=26 in each group. Mixed-effects model analysis with Bonferroni adjustment for multiple comparisons. Stars in blue and red indicate statistical significance in the within group comparison of the Standard and Long Limb groups respectively to baseline (*p<0.05, **p<0.01, ***p<0.001).

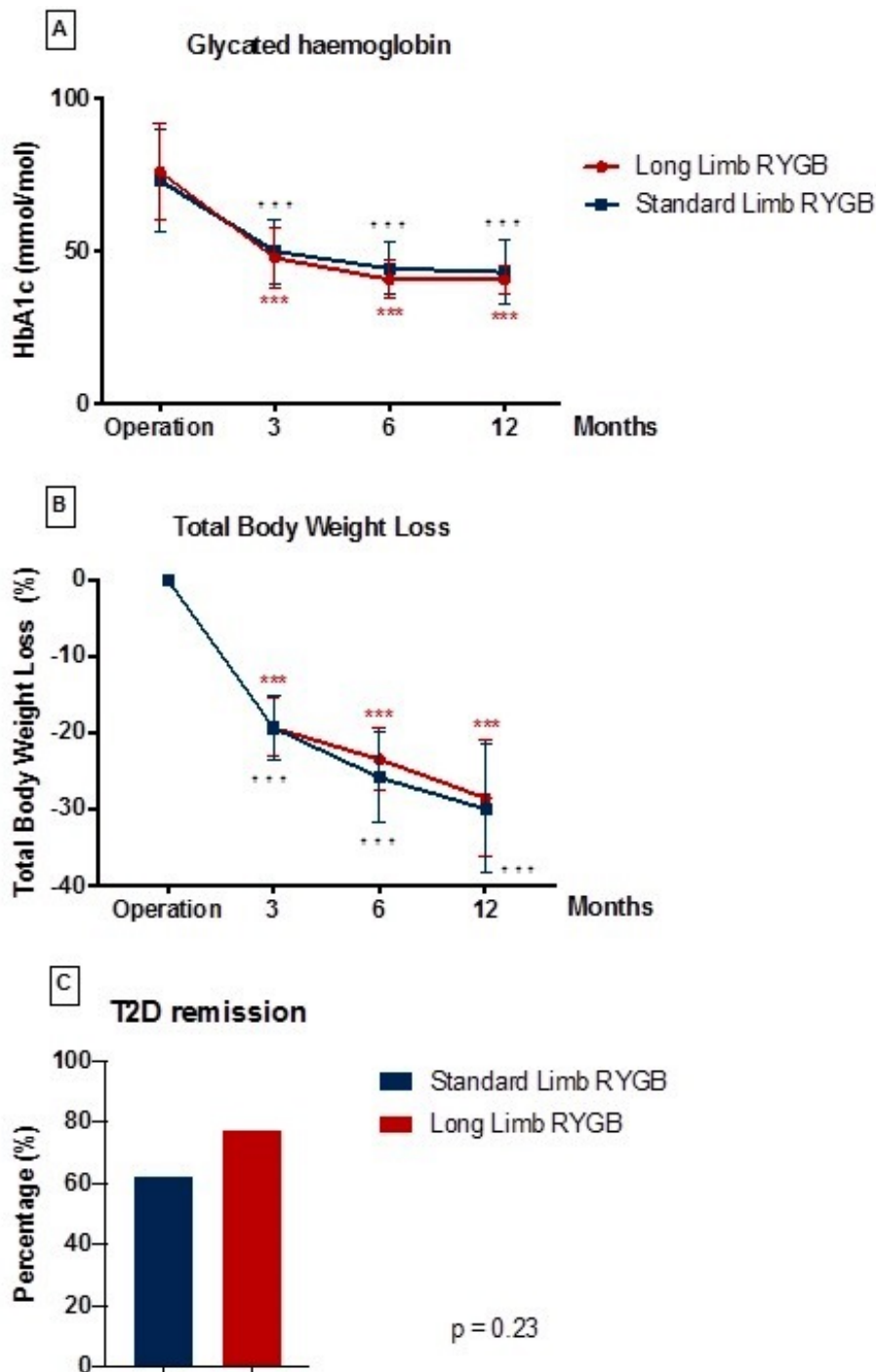


Figure S2. Glucose-lowering medications use

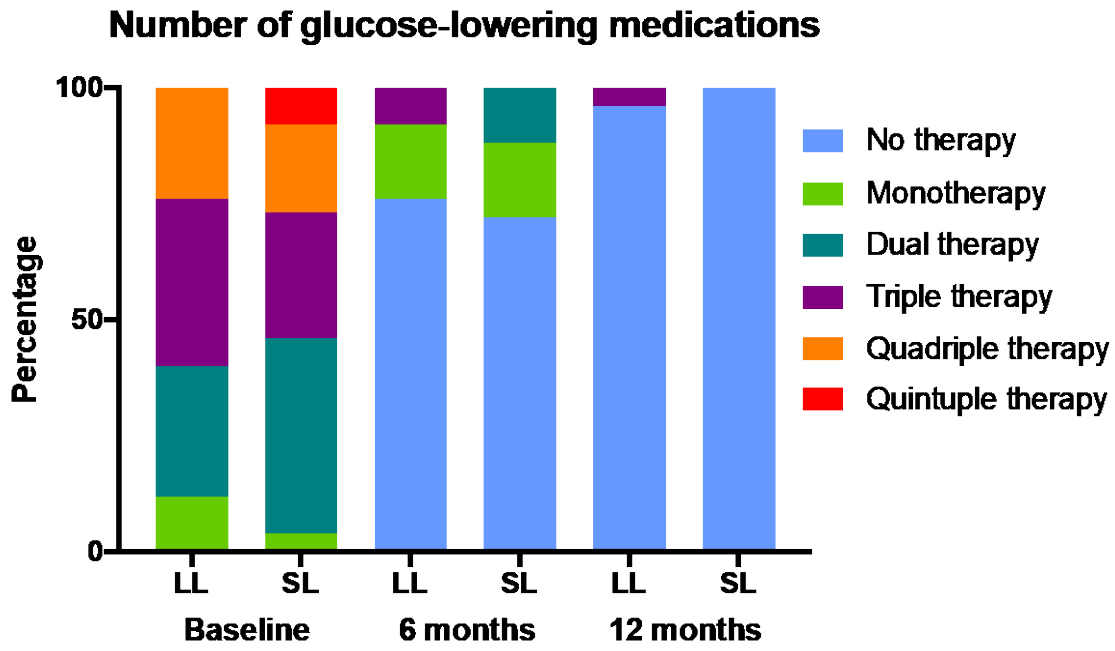


Table S4. Intra-operative small intestinal length measurements

	Long Limb RYGB n=25	Standard Limb RYGB n=26
Common channel length (cm)	360 [305-435] (250-660)	465 [320-528] (170-590)
Total small intestinal length (cm)	610 [555-685] (520-910)	615 [470-678] (320-740)
Biliopancreatic limb/total small intestinal length ratio (%)	25 [22-27] (16-29)	8 [7-11] (7-16)
Common channel/total small intestinal length ratio (%)	59 [55-64] (48-73)	76 [68-78] (53-80)
Operating time (minutes)	164 ± 51 (59-241)	146 ± 42 (79-250)
BPL/TSIL correlations with active GLP-1 peak at 2 weeks	r = 0.16 p = 0.45	r = 0.05 p = 0.84
BPL/TSIL correlations with GLP-1 AUC at 2 weeks	r = 0.18 p = 0.89	r = 0.07 p = 0.41

Continuous data presented as mean ± SD, range when normally distributed or median and 25-75% interquartile range, range when non-normally distributed. Correlations calculated with Pearson correlation coefficients RYGB – Roux-en-Y gastric bypass, BPL/TSIL - biliopancreatic limb to total small intestinal length ratio, AUC – area under the curve.

Table S5. Post-operative adverse events and complications

Adverse Event	Long Limb RYGB n=26	Standard Limb RYGB n=27
Cardiovascular	0	0
Gastrointestinal		
Anastomotic stricture	1	0
Anastomotic ulcer	0	1
Peri-operative bleeding	2	0
Gallstones	1	0
Abdominal pain	1	0
Laparotomy for purulent peritonitis	1	0
Gastritis	1	0
Diarrhoea	1	2
Constipation	0	1
Infections		
Wound infection	4	2
Pneumonia	4	2
Viral tonsillitis	1	0
Soft tissue and musculoskeletal		
Incisional hernia	1	0
Limb fracture	0	1
Nutritional and metabolic		
Intravenous treatment for dehydration	0	1
Acute kidney injury	0	2
Anaemia	2	2
Vasovagal	1	2
Hypoglycaemic episode	2	2
Adverse Events leading to hospitalisation	5 (in 3 participants)	4 (in 4 participants)
Clavien-Dindo classification of complications (grades)		
I	6	11
II	14	9
IIIa	1	0
IIIb	1	0
IV	1	0
V	0	0
Total	23	20

Clavien-Dindo classification: **Grade I:** Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside. **Grade II:** Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN). **Grade III:** Complications requiring surgical, endoscopic or radiological intervention; **Grade IIIa** - intervention not under general anaesthetic; **Grade IIIb** - intervention under general anaesthetic. **Grade IV:** Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs); **Grade IVa** - single-organ dysfunction (including dialysis); **Grade IVb** - multi-organ dysfunction. **Grade V:** Death of the patient.

Table S6. Mechanistic data: within groups comparisons of glucose, insulin and GLP-1 excursions during the MMTT and rate of glucose appearance and disappearance in clamps

Variable	Group	Pre-op visit	2 weeks post-op	20% weight loss	Mixed-effects analyses						Post hoc comparisons p value	
					Group effect		Visit effect		Group * Visit		Pre-op vs 2 weeks post-op	Pre-op vs 20% weight loss
					(DFn, DFd) = F value	P value	(DFn, DFd) = F value	P value	(DFn, DFd) = F value	P value		
AUC of plasma glucose (mmol·min/L)	Long Limb	2639 ± 659	1957 ± 653	1428 ± 430	(1, 48) = 1.3	0.27	(2, 96) = 96.1	<0.001	(2, 96) = 1.2	0.29	<0.001	<0.001
	Standard Limb	2876 ± 617	1938 ± 562	1642 ± 551							<0.001	<0.001
Peak of plasma glucose (mmol/L)	Long Limb	16.5 ± 4.1	13.9 ± 4.3	11.3 ± 2.4	(1, 48) = 1.9	0.17	(2, 96) = 32	<0.001	(2, 96) = 1.2	0.29	0.008	<0.001
	Standard Limb	17.5 ± 3.7	14.1 ± 3.4	13.4 ± 4.0							<0.001	<0.001
AUC of serum insulin (mU·min/L)	Long Limb	5128 ± 2833	6028 ± 3405	5657 ± 2831	(1, 48) = 0.3	0.59	(2, 95) = 4	0.02	(2, 95) = 0.4	0.64	0.20	0.81
	Standard Limb	5280 ± 2464	6259 ± 3088	6433 ± 3059							0.15	0.07
Peak of serum insulin (mU/L)	Long Limb	43.4 ± 27.0	76.1 ± 51.4	81.8 ± 38.3	(1, 48) = 0.4	0.54	(2, 95) = 40.5	<0.001	(2, 95) = 0.3	0.72	<0.001	<0.001
	Standard Limb	43.9 ± 23.0	84.1 ± 44.0	90.6 ± 45.7							<0.001	<0.001
AUC of active GLP-1 (pmol·min/L)	Long Limb	1274 ± 1347	4528 ± 1764	3812 ± 1327	(1, 48) = 1.8	0.18	(2, 79) = 104.8	<0.001	(2, 79) = 0.58	0.56	<0.001	<0.001
	Standard Limb	2330 ± 3832	5357 ± 3864	5259 ± 3613							<0.001	<0.001
Peak of active GLP-1 (pmol/L)	Long Limb	15.6 ± 13.2	61.9 ± 30.5	67.8 ± 22.0	(1, 48) = 1.7	0.20	(2, 96) = 100.7	<0.001	(2, 96) = 1.4	0.26	<0.001	<0.001
	Standard Limb	24.3 ± 33.1	77.9 ± 41.5	70.5 ± 31.3							<0.001	<0.001
Ra in low -dose insulin infusion (umol/min/kg)	Long Limb	4.99 ± 2.37	3.43 ± 1.38	2.56 ± 1.73	(1, 46) = 0.3	0.60	(2, 92) = 43.0	<0.001	(2, 92) = 0.1	0.92	<0.001	<0.001
	Standard Limb	5.21 ± 1.73	3.44 ± 0.93	2.84 ± 1.34							<0.001	<0.001
Ra in high-dose insulin infusion (umol/min/kg)	Long Limb	1.17 ± 1.99	0.67 ± 1.70	-0.97 ± 1.29	(1, 47) = 2.5	0.12	(2, 93) = 20.2	<0.001	(2, 93) = 1.2	0.30	0.88	<0.001
	Standard Limb	1.99 ± 2.37	0.65 ± 1.69	-0.03 ± 1.84							0.02	<0.001
Corrected for insulin concentration Ra	Long Limb	191.7 ± 83.3	115.6 ± 55.8	82.5 ± 59.4	(1, 46) = 0.64	0.43	(2, 92) = 59.5	<0.001	(2, 92) = 0.4	0.96	<0.001	<0.001
	Standard Limb	204.6 ± 66.0	121.1 ± 34.9	91.5 ± 49.6							<0.001	<0.001

in low-dose (umol/min/kg)												
Corrected for insulin concentration Ra in high-dose (umol/min/kg)	Long Limb	128.6 ± 237.2	85.3 ± 209.5	-89.4 ± 135.2	(1, 47) = 1.8	0.18	(2, 93) = 19	<0.001	(2, 93) = 1.5	0.23	1.00	<0.001
	Standard Limb	231.5 ± 277.6	67.8 ± 190.7	-3.7 ± 175.3							0.007	<0.001
Rd in low -dose insulin infusion (umol/min/kg)	Long Limb	10.58 ± 3.56	13.56 ± 4.21	16.48 ± 4.06	(1, 47) = 2.9	0.10	(2, 93) = 68.6	<0.001	(2, 93) = 0.6	0.57	<0.001	<0.001
	Standard Limb	9.79 ± 1.65	11.76 ± 2.90	15.24 ± 2.82							0.02	<0.001
Rd in high -dose insulin infusion (umol/min/kg)	Long Limb	19.13 ± 9.37	29.21 ± 9.90	38.13 ± 9.18	(1, 47) = 0.3	0.61	(2, 93) = 84.8	<0.001	(2, 93) = 0.2	0.83	<0.001	<0.001
	Standard Limb	18.49 ± 7.56	28.96 ± 9.08	36.12 ± 8.51							<0.001	<0.001
Corrected for insulin concentration Rd in low-dose (umol/min/kg)	Long Limb	0.29 ± 0.14	0.44 ± 0.22	0.52 ± 0.18	(1, 47) = 1.8	0.19	(2, 93) = 81.3	<0.001	(2, 93) = 3.0	0.05	<0.001	<0.001
	Standard Limb	0.26 ± 0.10	0.34 ± 0.10	0.50 ± 0.14							0.01	<0.001
Corrected for insulin concentration Rd in high-dose (umol/min/kg)	Long Limb	0.17 ± 0.08	0.30 ± 0.13	0.42 ± 0.17	(1, 47) = 0.07	0.79	(2, 93) = 90.7	<0.001	(2, 93) = 0.04	0.97	<0.001	<0.001
	Standard Limb	0.16 ± 0.08	0.30 ± 0.12	0.41 ± 0.11							<0.001	<0.001

Table S7. Within groups comparisons of glycated haemoglobin and weight loss

Variable	Group	Day of operation	3 months post-op	6 months post-op	12 months post-op	Mixed-effects analyses						Post hoc comparisons p value		
						Group effect		Visit effect		Group * Visit interaction		Op vs 3 months post-op	Op vs 6 months post-op	Op vs 12 months post-op
						(DFn, DFd) = F value	P value	(DFn, DFd) = F value	P value	(DFn, DFd) = F value	P value			
HbA1c (mmol/mol)	Long Limb	76 ± 16	48 ± 10	41 ± 6	41 ± 5	(1, 49) = 0.4	0.54	(3, 145) = 159.3	<0.001	(3, 145) = 1.5	0.22	<0.001	<0.001	<0.001
	Standard Limb	73 ± 17	50 ± 10	44 ± 8	43 ± 10							<0.001	<0.001	<0.001
Total Body Weight Loss (%)	Long Limb	0	19 ± 4	24 ± 4	29 ± 8	(1, 53) = 0.9	0.35	(3, 152) = 479.6	<0.001	(3, 152) = 0.7	0.56	<0.001	<0.001	<0.001
	Standard Limb	0	19 ± 4	26 ± 6	30 ± 8							<0.001	<0.001	<0.001

Continuous data presented as mean ± standard deviation. Statistical test used: mixed-effects analysis with Bonferroni adjustment for multiple comparisons in post-hoc analysis. p-values refer to comparing outcomes within Long Limb or Standard Limb at 2 weeks post-op visit and 20% weight loss visit. DFn – numerator degrees of freedom; DFd – denominator degrees of freedom. Ra: rate of glucose appearance. Rd: rate of glucose disappearance. Low: measured in the phase of low-dose insulin infusion. High: measured in the phase of high-dose insulin infusion. HbA1c – glycated haemoglobin.

Table S8. Key clinical parameters at baseline and at 1 year after intervention – per protocol analysis.

Characteristic	Long Limb Baseline n=25	Standard Limb Baseline n=25	Long Limb 1 year post-op n=25	Standard Limb 1 year post-op n=25	p value
Gender % (n)	Female 72% (18)	Female 60% (15)			
Ethnicity % (n)	68% White (17), 24% Asian (6), 8% Afro-Caribbean (2)	84% White (21), 8% Asian (2), 8% Afro-Caribbean (2)			
Age (years)	47 ± 8	50 ± 10			
Weight (kg)	120 ± 28	116 ± 18	87 ± 25	81 ± 13	0.87
BMI (kg/m²)	43 ± 8	41 ± 4	31 ± 7	29 ± 4	0.96
Total body weight loss (%)			29 ± 8	30 ± 9	0.52*
Waist circumference (cm)	128 ± 14	129 ± 12	100 ± 16	97 ± 12	0.46
Neck circumference (cm)	44 ± 6	44 ± 4	37 ± 5	37 ± 4	0.89
Total body fat percentage (%)	44 ± 6	43 ± 7	30 ± 9	27 ± 8	0.55
Total body fat free mass (kg)	66 ± 15	63 ± 13	56 ± 12	56 ± 10	0.54
Duration of T2DM (years)	6 [4-11]	8 [5-10]			
Number of glucose-lowering medications	3 [2-4]	3 [2-4]	0 [0-0]	0 [0-0]	n.s.
HbA1c (mmol/mol)	76 ± 16	72 ± 14	40 ± 5	44 ± 10	0.17

Rate of T2DM remission % (n)		76% (19)	60% (15)	0.36 [^]
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Categorical data presented as percentage (n). Continuous data presented as mean \pm SD when normally distributed or median [interquartile range] when non-normally distributed. Statistical tests used: logistic regression, *unpaired t-test, [^]Fisher's exact test. p-values refer to comparing Long Limb versus Standard Limb outcomes at 1 year post-operatively. RYGB: Roux-en-Y gastric bypass, BMI: Body Mass Index, T2DM – type 2 diabetes mellitus. HbA1c – glycated haemoglobin, n.s.: not significant.

CONSORT Flow Diagram

